Predicting Torsades de Pointes (TdeP) risk from data generated via high-throughput screening

Hitesh Mistry, Frances Brightman, Eric Fernandez, David Orrell, Jonathan Swinton, Christophe Chassagnole

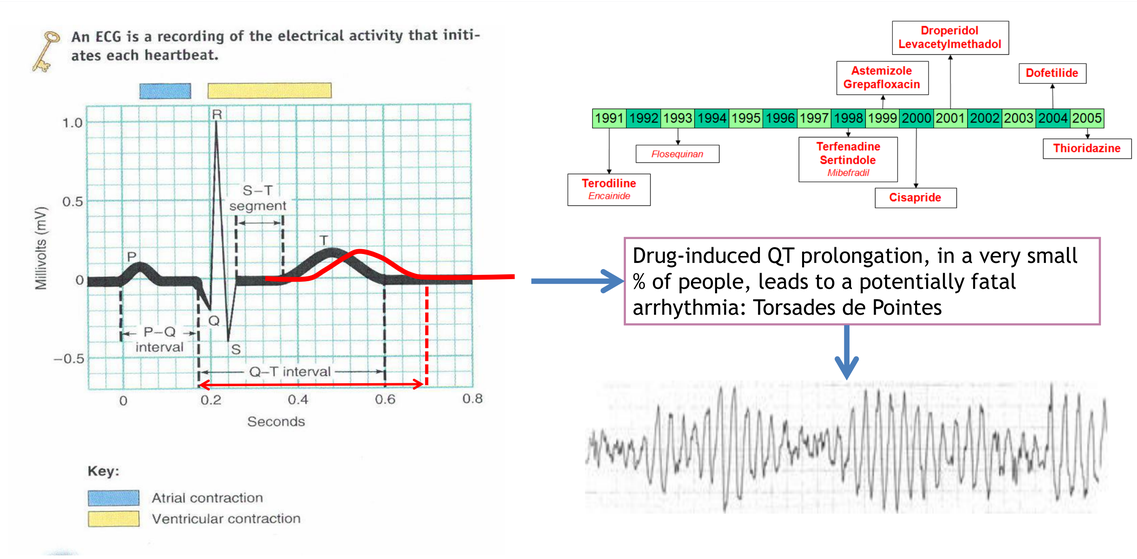
Physiomics plc, The Oxford Science Park, Oxford, OX4 4GA, United Kingdom. Tel. +44 (0)1865 784980. Email: hmistry@physiomics-plc.com

Compound Attrition[1]

Cardiovascular toxicity has been highlighted as one of the leading reasons for compound attrition all along the development pipeline over a number of years.

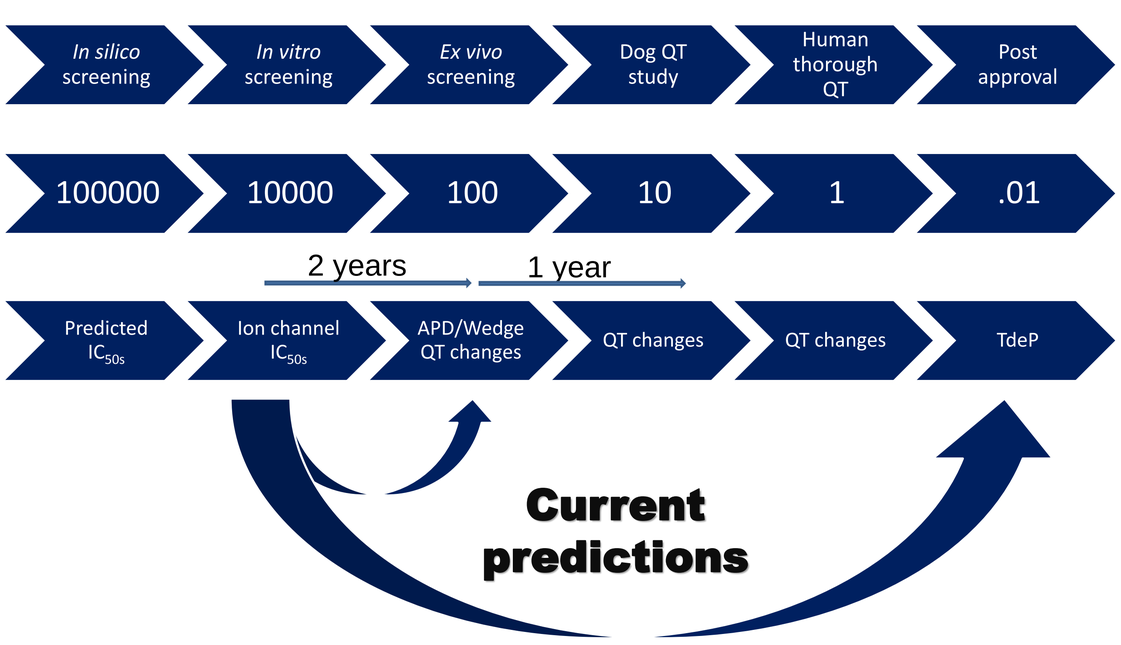
Phase	Non-clinical	Phase I	Phase I-III	Phase III/ post-approval	Post-approval	Post-approval	Post-approval
Information	Causes of attrition	Serious ADRs	Causes of attrition	ADRs on label	Serious ADRs	Withdrawal from sale	Withdrawal from sale
Source	Car (2006)	Sibille et al. (1998)	Olson et al. (2000)	BioPrint® (2006)	Budnitz et al. (2006)	Fung et al., (2001)	Stevens & Baker (2009)
Sample size	88 CDs stopped	1,015 subjects	82 CDs stopped	1,138 drugs	21,298 patients	121 drugs	47 drugs
Cardiovascular	27%	9%	21%	36%	15%	9%	45%
Hepatotoxicity	8%	7%	21%	13%	0%	25%	32%

QT/TdeP



1. TdeP is associated with QT prolongation.
2. QT prolongation is associated with prolongation of the action potential.
3. Prolongation of the action potential is associated with hERG block.
4. Screen everything for hERG!

All these associations are complex and have driven screening development for a number of other key ion channels, leading to the development of a TdeP screening process:



Within such a process predictions can be made regarding the effect in a future study.

Cardiac Models

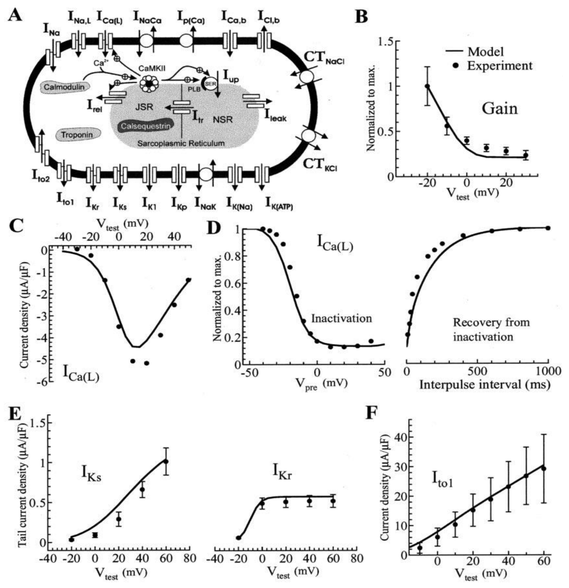
Large models – 10's ODEs, 100's of parameters

- High degree structural uncertainty

Models appear to be predictive:

- leave one out cross validation done by Mirams et al;[2]
- blind/external validation done by Davies et al.[3]

Can we figure out why and exploit it? – Build a semi-mechanistic model



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Simulation of multiple ion channel block provides improved early prediction of compounds' clinical torsadogenic risk

Gary R. Mirams[1*], Yi Cui[2], Anna Sher[1], Martin Fink[1], Jonathan Cooper[3], Bronagh M. Heath[4], Nick C. McMahon[2], David J. Gavaghan[3], and Denis Noble[1]

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First published December 23, 2011; doi:10.1152/ajpheart.00808.2011.

An in silico canine cardiac midmyocardial action potential duration model as a tool for early drug safety assessment

M. R. Davies,[1] H. B. Mistry,[1] L. Hussein,[2] C. E. Pollard,[2] J.-P. Valentin,[2] J. Swinton,[1*] and N. Abi-Gerges[2*]

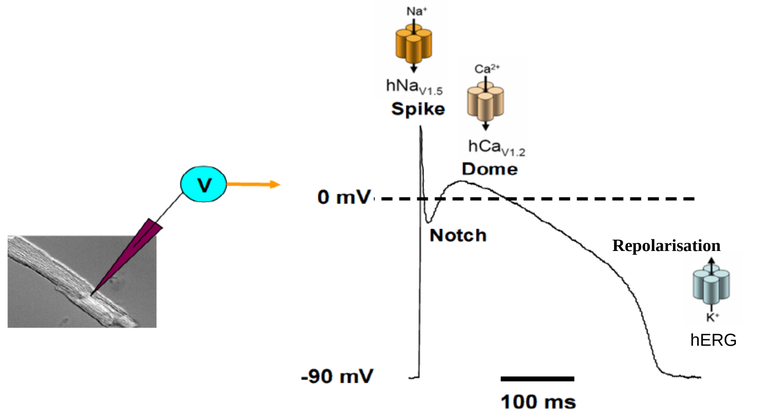
Redfern[4] Categories

Revised Redfern categories describe the number of reported incidences of TdeP:

1. Class 1a and III antiarryhthmics; generally associated with a large, but acceptable, risk of TdeP. Drugs that have been withdrawn from the market (by at least one major regulatory authority) due to unacceptable TdeP risk
2. Drugs with a measurable incidence of TdeP, or for which numerous case reports exist
3. Drugs for which there have been isolated case reports of TdeP
4. Drugs for which there have been no published reports of TdeP

Categories 1 and 2 from Redfern et al are grouped together as the degree of propensity is the same, only the indications are different[2].

Input Data



Extracted IC_{50s} data for three ion channels (hERG, hNav1.5, hCav1.2) from a single publication by ChanTest[5].

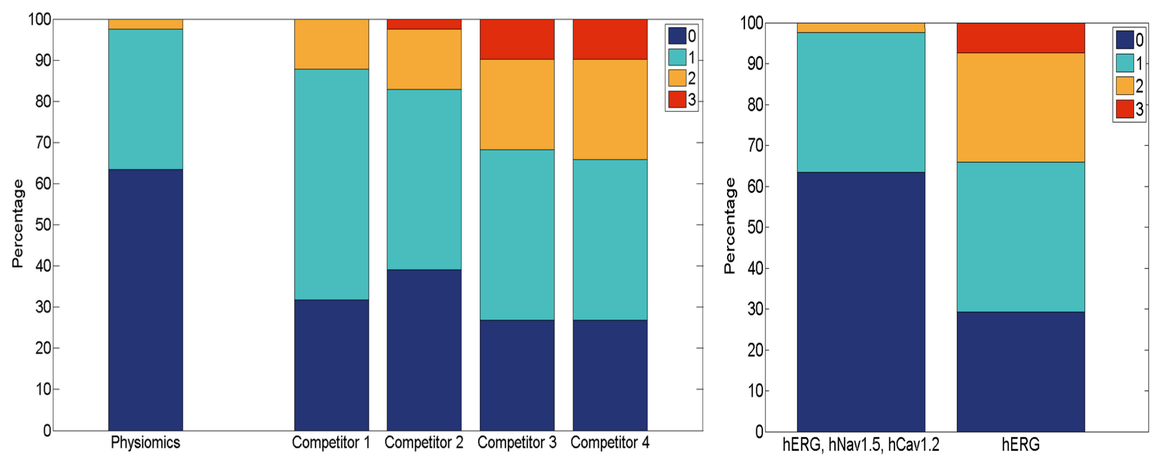
Methods

Input into models is IC_{50}/[EFTPC], where [EFTPC] is the mean effective therapeutic clinical concentration corrected for plasma protein binding. Output from each model is a single value fed into a classifier.

Models tested via a leave one out cross validation were:

1. Physiomics Model
2. Competitor 1: human model[6] – highlighted as a predictive model for TdeP categorisation[2]
3. Competitor 2: linear combination of ratios
4. Competitor 3: dog model[7] – highlighted as a predictive model for AP changes in dog[3]
5. Competitor 4: human model[8] - highlighted as a predictive model for QT changes in human[9]

Results



Figures show the error in classification: 0 - correct, 1 - one away, 2 - two away and 3 – three away.

1. Physiomics proprietary model is better than any current literature models.
2. Measuring more than hERG improves predictivity.

Conclusion

Physiomics has developed a cardiac toxicity prediction service using high-throughput screening data that is more predictive when assessed against published literature models. The model highlights that measuring more than hERG is important to assess torsadegenic risk. In addition to the TdeP prediction service we have also developed a dog toxicity prediction service. **Finally, the service we are providing could be part of a much larger framework to assess what additional information would be needed in addition to QTc prolongation to provide a more thorough quantitative assessment of a TQT study**.

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